1: Proc Natl Acad Sci U S A 2000 Jan 4;97(1):217-21 

# Mutations in a NIMA-related kinase gene, Nek1, cause pleiotropic effects including a progressive polycystic kidney disease in mice.

**Upadhya P, Birkenmeier EH, Birkenmeier CS, Barker JE.**

The Jackson Laboratory, Bar Harbor, ME 04609, USA.
pupadhya@aretha.jax.org

We previously have described a mouse model for polycystic kidney disease (PKD) caused by either of two mutations, kat or kat(2J), that map to the sam locus on chromosome 8. The homozygous mutant animals have a latent onse slowly progressing form of PKD with renal pathology similar to the human autosomal-dominant PKD. In addition, the mutant animals show pleiotropic effects that include facial dysmorphism, dwarfing, male sterility, anemia, anc cystic choroid plexus. We previously fine-mapped the kat(2J) mutation to a genetic distance of 0.28 +/- 0.12 centimorgan between D8Mit128 and D8Mit129. To identify the underlying molecular defect in this locus, we constructed an integrated genetic and physical map of the critical region surrounding the kat(2J) mutation. Cloning and expression analysis of the transcribed sequences from this region identified Nek1, a NIMA (never in mitosis A)-related kinase as a candidate gene. Further analysis of the Nek1 gene from both kat/kat and kat(2J)/kat(2J) mutant animals identified a partial internal deletion and a single-base insertion as the molecular basis for these mutations. The complex pleiotropic phenotypes seen in the homozygous mutant animals suggest that the NEK1 protein participates in different signaling pathways to regulate diverse cellular processes. Our findings identi a previously unsuspected role for Nek1 in the kidney and open a new avenue for studying cystogenesis and identifying possible modes of therapy.

PMID: 10618398 [PubMed - indexed for MEDLINE]

```
Query: 937  PHVLQNKPTLYRDISKNRLLSIKTFLYWTILGFSHAFIFFFGSYLLIGKDTSLLGNGQMF 996
            PHVLQNKPTLYRDISKNRLLSIKTFLYWTILGFSHAFIFFFGSYLLIGKDTSLLGNGQMF
Sbjct: 542  PHVLQNKPTLYRDISKNRLLSIKTFLYWTILGFSHAFIFFFGSYLLIGKDTSLLGNGQMF 601

Query: 997  GNWTFGTLVFTVMVITVTVKMALETHFWTWINHLVTWGSIIFYFVFSLFYGGILWPFLGS 1056
            GNWTFGTLVFTVMVITVTVKMALETHFWTWINHLVTWGSIIFYFVFSLFYGGILWPFLGS
Sbjct: 602  GNWTFGTLVFTVMVITVTVKMALETHFWTWINHLVTWGSIIFYFVFSLFYGGILWPFLGS 661

Query: 1057 QNMYFVFIQLLSSGSAWFAIILMVVTCLFLDIIKKVFDRHLHPTSTEKAQLTETNAGIKC 1116
            QNMYFVFIQLLSSGSAWFAIILMVVTCLFLDIIKKVFDRHLHPTSTEKAQLTETNAGIKC
Sbjct: 662  QNMYFVFIQLLSSGSAWFAIILMVVTCLFLDIIKKVFDRHLHPTSTEKAQLTETNAGIKC 721

Query: 1117 LDSMCCFPEGEAACASVGRMLERVIGRCSPTHISRSWSASDPFYTNDRSILTLSTMDSST 1176
            LDSMCCFPEGEAACASVGRMLERVIGRCSPTHISRSWSASDPFYTNDRSILTLSTMDSST
Sbjct: 722  LDSMCCFPEGEAACASVGRMLERVIGRCSPTHISRSWSASDPFYTNDRSILTLSTMDSST 781

Query: 1177 C 1177
            C
Sbjct: 782  C 782
```

>Q9Y2G3 A11B_HUMAN Q9Y2G3 POTENTIAL PHOSPHOLIPID-TRANSPORTING ATP
Length = 672

Score = 1350 bits (3495), Expect = 0.0
Identities = 672/672 (100%), Positives = 672/672 (100%)

```
Query: 506  DCTGDGPWQSNLAPSQLEYYASSPDEKALVEAAARIGIVFIGNSEETMEVKTLGKLERYK 565
            DCTGDGPWQSNLAPSQLEYYASSPDEKALVEAAARIGIVFIGNSEETMEVKTLGKLERYK
Sbjct: 1    DCTGDGPWQSNLAPSQLEYYASSPDEKALVEAAARIGIVFIGNSEETMEVKTLGKLERYK 60

Query: 566  LLHILEFDSDRRRMSVIVQAPSGEKLLFAKGAESSILPKCIGGEIEKTRIHVDEFALKGL 625
            LLHILEFDSDRRRMSVIVQAPSGEKLLFAKGAESSILPKCIGGEIEKTRIHVDEFALKGL
Sbjct: 61   LLHILEFDSDRRRMSVIVQAPSGEKLLFAKGAESSILPKCIGGEIEKTRIHVDEFALKGL 120

Query: 626  RTLCIAYRKFTSKEYEEIDKRIFEARTALQQREEKLAAVFQFIEKDLILLGATAVEDRLQ 685
            RTLCIAYRKFTSKEYEEIDKRIFEARTALQQREEKLAAVFQFIEKDLILLGATAVEDRLQ
Sbjct: 121  RTLCIAYRKFTSKEYEEIDKRIFEARTALQQREEKLAAVFQFIEKDLILLGATAVEDRLQ 180

Query: 686  DKVRETIEALRMAGIKVWVLTGDKHETAVSVSLSCGHFHRTMNILELINQKSDSECAEQL 745
            DKVRETIEALRMAGIKVWVLTGDKHETAVSVSLSCGHFHRTMNILELINQKSDSECAEQL
Sbjct: 181  DKVRETIEALRMAGIKVWVLTGDKHETAVSVSLSCGHFHRTMNILELINQKSDSECAEQL 240

Query: 746  RQLARRITEDHVIQHGLVVDGTSLSLALREHEKLFMEVCRNCSAVLCCRMAPLQKAKVIR 805
            RQLARRITEDHVIQHGLVVDGTSLSLALREHEKLFMEVCRNCSAVLCCRMAPLQKAKVIR
Sbjct: 241  RQLARRITEDHVIQHGLVVDGTSLSLALREHEKLFMEVCRNCSAVLCCRMAPLQKAKVIR 300

Query: 806  LIKISPEKPITLAVGDGANDVSMIQEAHVGIGIMGKEGRQAARNSDYAIARFKFLSKLLF 865
            LIKISPEKPITLAVGDGANDVSMIQEAHVGIGIMGKEGRQAARNSDYAIARFKFLSKLLF
Sbjct: 301  LIKISPEKPITLAVGDGANDVSMIQEAHVGIGIMGKEGRQAARNSDYAIARFKFLSKLLF 360

Query: 866  VHGHFYYIRIATLVQYFFYKNVCFITPQFLYQFYCLFSQQTLYDSVYLTLYNICFTSLPI 925
            VHGHFYYIRIATLVQYFFYKNVCFITPQFLYQFYCLFSQQTLYDSVYLTLYNICFTSLPI
Sbjct: 361  VHGHFYYIRIATLVQYFFYKNVCFITPQFLYQFYCLFSQQTLYDSVYLTLYNICFTSLPI 420

Query: 926  LIYSLLEQHVDPHVLQNKPTLYRDISKNRLLSIKTFLYWTILGFSHAFIFFFGSYLLIGK 985
            LIYSLLEQHVDPHVLQNKPTLYRDISKNRLLSIKTFLYWTILGFSHAFIFFFGSYLLIGK
Sbjct: 421  LIYSLLEQHVDPHVLQNKPTLYRDISKNRLLSIKTFLYWTILGFSHAFIFFFGSYLLIGK 480
```